



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/565</b>	<b>A2</b>	(11) International Publication Number: <b>WO 96/36339</b> (43) International Publication Date: 21 November 1996 (21.11.96)
<p>(21) International Application Number: PCT/US96/06078</p> <p>(22) International Filing Date: 1 May 1996 (01.05.96)</p> <p>(30) Priority Data: 08/440,726 15 May 1995 (15.05.95) US 08/487,471 7 June 1995 (07.06.95) US</p> <p>(71) Applicant: BETH ISRAEL HOSPITAL [US/US]; 330 Brookline Avenue, Boston, MA 02215 (US).</p> <p>(72) Inventor: MANTZOROS, Christo, S.; 210 Sherman Road, Newton, MA 02158 (US).</p> <p>(74) Agents: REMILLARD, Jane, E. et al.; Lahive &amp; Cockfield, 60 State Street, Boston, MA 02109 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i></p>
<p>(54) Title: USE OF DIHYDROTESTOSTERONE COMPOUNDS FOR TREATING MALE SEXUAL DYSFUNCTION</p> <p>(57) Abstract</p> <p>A method for treating sexual dysfunction in a subject, comprising increasing dihydrotestosterone (DHT) concentrations in the subject to effectively treat the sexual dysfunction is disclosed. Methods of the invention can be used for prophylactic and/or therapeutic treatment of sexual dysfunctions.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Larvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## USE OF DIHYDROTESTOSTERONE COMPOUNDS FOR TREATING MALE SEXUAL DYSFUNCTION

### Background of the Invention

5           Impaired sexual function, such as impotence and decreased libido, is relatively common in middle aged and elderly men. The percentages of these men that exhibit impaired sexual function is between 9% and 30%. Sexual dysfunction has been linked to low male hormone levels. For example, when normal men are made hypogonadic (experimental induction of low male hormone levels) they develop impaired sexual function.

10

          It is believed that testosterone regulates sexual behavior in humans, although this belief has never been confirmed experimentally. Testosterone replacement treatment, in the form of intramuscular injections, has been shown to restore sexual function. It has also been shown that subnormal libido and sexual function due to either induced or spontaneous  
15   hypogonadism improve with testosterone treatment. See Weinbauer *et al.*, Acta Endocrinol (Copenh) 122, 432-442 (1990), and Bragatell *et al.*, J. Clin. Endo. Metabol 78, 711-716 (1994). However, testosterone replacement therapy often has adverse side effects, including feminizing effects of estradiol, such as enlargement of the breasts (gynecomastia) and fluid retention.

20

          Testosterone is converted in the human body to dihydrotestosterone (DHT) and estradiol. It remains unclear whether sexual behavior is regulated by testosterone itself or by one of its metabolites, such as DHT. Although normal levels of DHT cause no serious side effects, supraphysiological levels can cause benign prostatic hypertrophy and possibly other serious medical conditions. In particular, it has been shown that the threshold for  
25   prostate growth (initiation of prostatic hyperplasia) is approximately 1 nanogram of DHT per gram of prostatic tissue. Therefore, while physiological replacement therapy of DHT might have favorable effects, supraphysiological levels of DHT or testosterone replacement therapy to treat sexual dysfunction might result in significant health impairments.

30

### Summary of the Invention

          The present invention provides a method for treating sexual dysfunction of a subject by increasing bioactive dihydrotestosterone (DHT) plasma levels. Preferably, the levels are increased from an undetectable, low abnormal, or even low normal level to within  
35   the normal range, without substantially exceeding the normal range (i.e., achieving supraphysiological concentrations of DHT).

          The invention is based, at least in part, on the discovery that achieving physiological concentrations of dihydrotestosterone (while avoiding adverse side effects

which can result from supraphysiological concentrations of DHT) is an effective means for treating sexual dysfunction in a subject. Increase of plasma DHT to desired levels at which sexual function is restored can be achieved by administering to a subject exogenous DHT or a derivative thereof in a suitable form. Alternatively, levels of DHT can be increased by  
5 inhibiting metabolic breakdown and excretion of endogenous DHT, or by increasing internal production of DHT.

The methods provided by the present invention can be prophylactic and/or therapeutic treatments of sexual dysfunction. The methods provide the advantages of  
10 allowing a physician to recognize important determinants in the treatment of sexual dysfunction, and allowing the physician to adequately diagnose and treat the dysfunction. The method of the present invention also can be advantageous over conventional procedures since it is easily adaptable to existing treatments and thus can be used in combination  
therapies.

15

The present invention provides a method for treating sexual dysfunction in a subject by increasing physiological concentrations of bioactive DHT to a serum level which corrects the dysfunction. The present invention further pertains to compositions for treating sexual dysfunction in a subject. Other aspects of the invention include packaged compounds  
20 that include instructions relating to use, dosage and regimen.

### **Brief Description of the Figures**

Figure 1 is a tabulation of the demographic lifestyle and endocrine correlates  
25 of the weekly number of orgasmic events of the subjects.

Figure 2 is a tabulation of an evaluation of dihydrotestosterone, androstenione and age as predictors of orgasmic events

### **Description of Illustrated Embodiments**

The present invention pertains to a method of treating sexual dysfunction in a subject by achieving physiological concentrations of bioavailable dihydrotestosterone (DHT). The term "treating" sexual dysfunction is intended to include preventing, inhibiting,  
35 reducing, or delaying the progression and/or effects of the dysfunction.

The language "sexual dysfunction" is intended to include dysfunctions associated with the sexual activity and/ or sexual response of the subject. Examples of sexual dysfunctions include erectile inadequacy, inhibited male orgasm, decreased libido or sexual

drive, sexual arousal dysfunction, and impotence. The sexual dysfunction can be a naturally occurring dysfunction, a trauma induced dysfunction, or a dysfunction that arises from the purposeful inducement of the dysfunction, such as by the administration of a selected compound to the subject.

5

Sexual dysfunction disorders can result in the inhibition in the sexual response cycle which may occur at one or more sexual response phases, e.g., desire, arousal and performance, or their respective components. Sexual dysfunction can involve both subjective parameters of sexual functioning, e.g., desire, arousal, and pleasure, as well as the objective  
10 parameters of sexual functioning, e.g., performance and orgasm. Sexual dysfunction can also involve fertility, such as decreased semen volume and quality (i.e., sperm counts, motility etc.). In certain situations, either the subjective or objective set of parameters may be classified as being primary, e.g., with effective performance never having been experienced in any situation, or secondary, e.g., dysfunctions acquired after a period of normal  
15 functioning. Secondary parameters are often medication induced (e.g., chemotherapy, radiation etc.) or the result of other medical conditions. Sexual dysfunction may also be characterized as generalized or limited to certain situations or with certain partners.

The etiology of sexual dysfunction can also comprise psychological factors, interpersonal and situational causes, physical factors, and pharmacological agent side effects.  
20 Since sexual dysfunction can result from a variety of underlying causes, including those set forth above, the dihydrotestosterone compound of the present invention may be utilized alone or along with other treatment modalities.

25 The term "subject" is intended to include mammals having or being susceptible to sexual dysfunction. Examples of such subjects include humans, pigs, cows, horses, rats, mice, domestic animals, zoo animals, and rare or endangered species.

The term "administering" is intended to include all routes of administration  
30 including injection (subcutaneous, intramuscular, intravenous, parenterally, intraperitoneally, intrathecal, etc.), oral, sublingual (e.g., cyclodextrin drug complexes), transdermal, and slow release microspheres. The injection can be bolus injections or can be continuous infusion. Depending on the route of administration, the dihydrotestosterone compound can be coated with or disposed in a selected material to protect it from natural conditions which may  
35 detrimentally affect its ability to perform its intended function. The agent can be encapsulated by a biocompatible and/or biodegradable microparticle, e.g., a polymeric matrix, to effectuate a time-controlled release of the bound agent.

For transdermal administration, the dihydrotestosterone compound can be incorporated into a film or patch which is applied at regular intervals (e.g., daily), typically to the scrotal skin. This preparation permits maintenance of plasma concentrations of the agent within the normal range.

5

For oral administration, the compound may be formulated into a capsule (hard or soft) or tablet that is prepared by conventional techniques with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose), fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate), lubricants (e.g., magnesium stearate, talc or silica), disintegrants (e.g., potato starch or sodium starch glycolate), or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional techniques with pharmaceutically acceptable additives, such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats), emulsifying agents (e.g., lecithin or acacia), and non-aqueous vehicles (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid).

20

The dihydrotestosterone compound can be administered alone, or in conjunction with other suitable agents or with a pharmaceutically acceptable carrier, or both. The dihydrotestosterone compound can be administered to the subject prior to the onset of the sexual dysfunction, during the dysfunction, or after the onset of the sexual dysfunction. The dihydrotestosterone compound can also be administered as a prodrug which is converted to its active form *in vivo*.

25

The language "pharmaceutically acceptable carrier" is intended to include substances capable of being coadministered with the dihydrotestosterone compound, and which allows it to perform its intended function of treating sexual dysfunction. Examples of such carriers include solutions, solvents, dispersion media, delay agents, emulsions and the like. The use of such media for pharmaceutically active substances are well known in the art. Any other conventional carrier suitable for use with the selective condition inhibitory agent also falls within the scope of the present invention.

35

The language "effective amount" of the dihydrotestosterone compound is that amount necessary or sufficient to treat sexual dysfunction in the subject. The effective amount can vary depending on such factors as the type and severity of the sexual dysfunction being treated, the potency of the dihydrotestosterone compound, the residence time of the

agent within the subject, the size and age of the subject, and the mode of application of the agent. For example, the type of dihydrotestosterone compound can affect what constitutes an effective amount.

5 One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the compound without undue experimentation. For example, DHT replacement therapy (i.e., administration of an exogenous DHT compound) aimed at achieving physiological DHT levels can be monitored by currently available laboratory techniques, including laboratory determinations of blood  
10 level DHT. Additionally, the *in vivo* assays described below or an assay similar thereto (e.g., differing in choice of subject or age of the subject) can be used to determine an "effective amount" of the compound. The ordinarily skilled artisan would select an appropriate amount of the compound for use in the aforementioned *in vivo* assays.

15 The regimen of administration also can affect what constitutes an effective amount. The dihydrotestosterone can be administered to the subject prior to, simultaneously with, or after the onset of the sexual dysfunction. Further, several divided dosages, staggered dosages, as well as a time-controlled release of the agent in selected dosages, can be administered daily or sequentially, or the dose can be continuously infused depending upon  
20 the type of compound employed and the preferred mode of administration to the subject. Further, the dosages of the agent can be proportionally increased or decreased as indicated by the exigencies of the therapeutic situation.

The language "dihydrotestosterone compound" is intended to include  
25 dihydrotestosterone (DHT) and analogues of DHT which have been chemically modified to retard the rate of catabolism or to enhance the androgenic potency of DHT. These chemical modifications of DHT include esterification of the 17 $\beta$ -hydroxyl group with any of several carboxylic acids to decrease the polarity of the molecule, making it more soluble in lipid vehicles used for injection and slowed release into the bloodstream. The longer the carbon  
30 chain in the ester, the more lipid soluble the steroid becomes and the more prolonged is the release of the steroid *in vivo*. Other dihydrotestosterone esters include those derived from aliphatic carboxylic acids, derivatives and analogues of dihydrotestosterone, short chain esters of DHT (e.g., propionate and cypionate) as well as long and branched chain esters, and esters of DHT (e.g., 3-alkyloxy form of DHT). Other modifications of DHT which are  
35 encompassed by the invention also include alkylation at the 17 $\alpha$  position. Such alkylated derivatives are slowly catabolized by the liver. The alkyl group is not removed metabolically. Therefore, the alkylated derivative mediates the action of the hormone within cells.

Preferred compounds of the invention include 5 $\alpha$ -dihydrotestosterone (5 $\alpha$  DHT), 5 $\beta$ -dihydrotestosterone (5 $\beta$  DHT), and esters, analogues and/or derivatives thereof, such as 5 $\alpha$  and 5 $\beta$  reduced analogues, biocompatible derivatives, such as alkanolic acid derivatives, 17 alkylated (e.g., methylated) derivatives of 5 $\alpha$  and 5 $\beta$  DHT, and 5 $\alpha$  and 5 $\beta$  DHT esters that are hydrolyzable *in vivo*. Examples of aliphatic carboxylic acids, from which the foregoing esters are derived, preferably include pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, undecenoic acid, palmitic acid and the branched chain and cyclic analogues of these acids. The manufacture of these esters is set forth in U.S. Patent Nos. 4,098,802 and 4,220,599 of van der Vies, which are both herein incorporated by reference.

The present invention further pertains to packaged dihydrotestosterone compounds packaged with instructions for using the compound as a treatment for sexual dysfunction. The instructions would provide selected information such as the appropriate dose of the compound or the appropriate regimen.

Another aspect of the present invention provides a method for treating sexual dysfunction in a subject, comprising increasing DHT concentrations in the subject to effectively treat the sexual dysfunction. In particular, the invention aims at increasing bioactive dihydrotestosterone (DHT) plasma levels from an undetectable, low abnormal, or even low normal level to within the normal range, without substantially exceeding the normal range (i.e., achieving supraphysiological concentrations of DHT). The term "normal range", as used herein, means the range of DHT serum levels measured for individuals of a given population whose sexual function (e.g., sexual desire, sexual performance, and fertility) is normal. This range may vary depending on variables, such as age, demographics and lifestyle for any given population and can be determined as described below in the exemplification. In general, a normal range is the mean for a given population with a standard deviation of 0.6, preferably 0.4, and more preferably about 0.2. As an example, in healthy males ranging from 18 to 22 years of age tested in the studies described below in the exemplification section, the mean serum DHT level was 0.787 ng/ml and a standard deviation of 0.207.

Accordingly, the term "low abnormal level" of DHT, as used herein, means below the normal range of serum level DHT, as previously defined. The term "low normal level" of DHT, as used herein, means above the lower limit of the normal range of serum level DHT, as previously defined, but not above the mean for the normal range. The term "not substantially exceeding the normal range", as used herein, means serum DHT levels above the normal range, as previously defined, but not high enough to cause significant

adverse effects, such as those associated with supraphysiological concentrations of DHT, including but not limited to benign prostatic hypertrophy.

5 In one embodiment of the invention, serum level DHT is increased in a sexually dysfunctional patient by administering to the patient an effective amount of an exogenous dihydrotestosterone compound to treat the sexual dysfunction. In a preferred embodiment, the DHT compound is administered in a controlled, sustained release manner, for example, by a transdermal therapeutic system (TTS) (e.g., a transdermal patch).

10 In another embodiment of the invention, serum level DHT is increased in a sexually dysfunctional patient by inducing accumulation of endogenous DHT (i.e., DHT which is naturally produced within the patient). Accumulation of endogenous DHT can be induced in a number of different ways. For example, metabolism of endogenous DHT can be inhibited by, for example, inhibition of enzymes which convert DHT to other hormones.  
15 These enzymes include but are not limited to sulfatases, glucuronidases, and other hepatic enzymes responsible for metabolism of hormones. The activity of these enzymes can be reduced or abolished by, for example, chemical or biological means.

20 Alternatively, accumulation of endogenous DHT can be induced by promoting production of endogenous DHT. This can be done by a number of different means, including pharmacological, chemical, or genetic means. For example, a patient can be administered an enzyme which causes conversion of DHT precursors, such as testosterone, to DHT. Such enzymes include 5- $\alpha$ -reductases and analogues thereof which convert testosterone to DHT. Alternatively, DHT can be produced *in vivo* by causing its release from, or by preventing its  
25 binding to, certain androgen binding proteins with which DHT is normally associated with *in vivo*. These androgen binding proteins include, for example, sex hormone binding globulin (SHBG). In one embodiment, DHT can be prevented from binding to such androgen binding proteins by administering an analogue of DHT which effectively competes with DHT for binding to the androgen binding protein.

30 The invention is further illustrated by the following example, which should not be construed as further limiting. The contents of all references, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated by reference.

35

### Example

#### Materials and Methods

5                   The subjects were 100 male army recruits, 18-22 years old, who consented having a single blood sample drawn during their first day in the army. The subjects were healthy and were taking no medication.

10                   The participants responded to an interviewer-administered questionnaire that covered basic demographic and lifestyle variables. Specifically, the participants were asked to indicate their age in completed years, height in centimeters, weight in kilograms and educational level in years of schooling. Quetelet index (body mass index) was calculated as weight/height<sup>2</sup>. In addition, subjects were asked to indicate whether they were smokers, and if so, the daily number of cigarettes consumed. Information was also provided concerning  
15                   usual coffee drinking in cups per day, and usual alcohol intake in glasses per day. Greek (Turkish) coffee was the type consumed by the overwhelming majority of subjects, whereas ethanol consumed in the standard measures of most drinks is approximately the same for wine, beer and spirits. Voluntary physical activity was recorded in hours per day but no attempt was made to weight it according to level of intensity. Finally the subjects were asked  
20                   to indicate the average number of orgasmic events per week over the last month. Recalled number of orgasmic events per week has been previously shown to represent a major and reliable expression of male sexual behavior (Davidson et al., J. Clin Endocrinol Metab 57, 71-77 (1983)). It was made clear to the subjects that one objective was to assess the total number of orgasmic events, rather the mode of their initiation, in the context of sexual  
25                   intercourse, masturbation or spontaneous nocturnal orgasmic events. This approach was adopted to optimize the validity of the response since young men in the Greek culture environment could have been tempted to overreport orgasmic events during intercourse and underreport ones during masturbation.

30                   Blood samples for the hormone determinations were centrifuged immediately and serum was frozen at -34C until determination. Serum hormone levels were determined by commercially available RIA kits (Coat-a-Count, DPC, Los Angeles, CA for testosterone and dehydroepiandrosterone sulfate, Amersham Intl. UK for dihydrotestosterone, EIRRIA, Switzerland for estradiol and estrone. Buhlman Lab Ltd., Italy for delta-4-androstendione  
35                   and Biodata Spa, Switzerland for Sex Hormone Binding Globulin). The sensitivity of the assays was as follows: testosterone 4ng/dl, estrone 8 pg/ml, estradiol 6.2 ph/ml, delta-4-androstendione 0.02 ng/ml, dihydrotestosterone 5 ph/ml, dehydroepiandrosterone sulfate 21 ng/ml. The coefficients of variation in the range of values measured were 5.2% for dihydrotestosterone, 4.5-5.5% for dehydroepiandrosterone sulfate, 5.8% for testosterone, 5-

8% for delta-4-androstendione, 5-6% for estradiol and estrone, 2.8-6.9% for sex hormone binding globulin.

Statistical analysis was done by modeling weekly number of orgasmic events as a function of demographic, lifestyle and endocrine variables. Weekly number of orgasmic events was approximately normally distributed with a mean of 3.9 and a standard deviation of 1.9. For eight individuals there were one or more missing values and these individuals were excluded from the analysis.

## 10 Results

Table 1 of Figure 1 shows representative values of the demographic and lifestyle variables. The mean weekly number of orgasmic events in this study was 3.9, the standard deviation 1.9, the median and the mode 3.5, the range was 0 to 11 and the first and third quintiles were 2.2 and 5.5 respectively. Simple and multiple regression-deprived regression coefficients of the weekly number of orgasmic events regressed on these variables are also known in Table 1. Only age is a statistically significant predictor of the frequency of orgasmic events. Table 1 also presents representative values of the endocrine variables as well as simple and multiple regression-deprived regression coefficients of weekly number of orgasmic events regressed on these hormones. Only dihydrotestosterone and perhaps delta-4-androstendione appear to be independent predictors of the weekly number of orgasmic events. By contrast, testosterone was unrelated to the frequency of the orgasmic events. There were no colinearity problems in the statistical analysis. The highest value of the Pearson correlation coefficient between any two of the hormones studied were 0.27 for dihydrotestosterone with delta-4-androstendione.

In table 2 of Figure 2, the weekly frequency of orgasmic events is regressed on age, dihydrotestosterone and delta-4-androstendione, that is the variables that appear to be the important predictors of the frequency of orgasmic events on the basis of the models presented in tables 1 and 2. Age and dihydrotestosterone remain statistically significant and independent predictors of the frequency of orgasmic events whereas the partial regression coefficient for delta-4-androstendione is reduced from .644 to .512 and the corresponding significance level is weakened from 0.063 to 0.105. The values of the Pearson correlation coefficients between the weekly frequency of orgasmic events on one hand and dihydrotestosterone and age on the other were .28 and .30 respectively. Regressing the frequency of orgasmic events on free hormone indexes (calculated as the ratio of testosterone, estradiol or estrone over sex hormone binding globulin) generated essentially identical results; age ( $p=.001$ ) and dihydrotestosterone ( $p=.006$ ) remained the only statistically significant predictors of the weekly frequency of orgasmic events.

Among androgens, testosterone has been found to be a determinant of sexual function in rodents and non-human primates (Weinbauer et al., Acta Endocrinol 122, 432-442 (1990)). The effect of sex steroids other than testosterone has not been adequately studies in humans (Weinbauer et al., cited supra; Bagatell et al., J. Clin Endo Metabol 78, 711-716 (1994); and Davidson et al., J. Clin Endocrinol Metab 57, 71-77 (1983)). Men with hypogonadism due to pituitary or testicular failure have decreased libido and sexually activity that can be restored with testosterone replacement treatment. It is not known whether supplementation with testosterone improves sexual activity by increasing levels of circulating testosterone or through seroconversion to the much more potent dihydrotestosterone (Bancroft, Clin Obstet Gynecol 7, 253-281 (1980). In normal men, marked testosterone reduction due to spontaneous or induced hypogonadism by administration of luteinizing hormone releasing hormone agonist (see Bagatell, cited supra) has been associated with impaired sexual behavior, which was restored with testosterone treatment. Neither testosterone nor any testosterone metabolite concentrations were measured in these studies, making it difficult to identify the active androgenic compound. In most cross-sectional studies in eugonadal adult men no correlation has been found between sexual activity and circulating levels of testosterone, although weak positive (see Knussmann et al., Archives Sexual Behavior 15, 429-445 (1986)) and negative (Kraemer et al., Archives Sexual Behavior 5, 125-132 (1976)) correlations have also been reported in small studies. Therefore, there exists equivocal evidence for the role of testosterone in determining sexual activity of healthy adults, and virtually no evidence concerning the possible role of dihydrotestosterone.

The results of this study strongly support the hypothesis that dihydrotestosterone is the active hormone for male sexual function as reflected in the frequency of orgasmic events. An increase of dihydrotestosterone by two standard deviations (.4 ng/ml) is associated with an increase of the weekly number of orgasmic events by at least one, and conceivably more depending on the extend of biologically generated variation and consequent misclassification. Additionally, within the age range studies, a difference of three years corresponds to an increase of the weekly number or orgasmic events by about two; this increase is likely to reflect socially conditioned enhancement of opportunities with increasing age.

Only orgasmic events were evaluated in this investigation and no attempt was made to ascertain other aspects of male sexual behavior (Anderson et al., J. Clin Endocrinol Metab 75, 1503-1507 (1992)). However, previous studies have found that self reported frequency of orgasmic events in men is a highly reliable method for the evaluation of the effect of androgens on sexual activity and that tends to remain stable overtime (see Davidson, cited supra, and Tsitouras, Endocrinol Metabol Clin 16, 1045-1059 1987)). There is

undoubtedly misclassification in the reporting of the frequency of orgasmic events as well as in the laboratory determinants of dihydrotestosterone and other hormones. The corresponding errors, however, are clearly uncorrelated since laboratory tests were blindly performed and the personnel involved has no knowledge of the identity of the subjects or their questionnaire data. Nondifferential misclassification can bias the regression coefficients towards the null values but the extend of this misclassification was not smaller for dihydrotestosterone than for other hormones.

It appears that in normal young adults the potent testosterone metabolite dihydrotestosterone, which binds much more avidly with the androgen receptor (Mooradjian et al., Endocr Rev 8, 1-28 (1987)), is the most important or perhaps the only important androgen in determining male sexual behavior as reflected in the frequency of orgasmic events, while physiological levels of serum estrogen and adrenal steroids do not appear to play an independent role of comparable importance.

15

### **EQUIVALENTS**

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

20

**CLAIMS**

1. A method for treating sexual dysfunction in a subject, comprising increasing DHT concentrations in the subject to effectively treat the sexual dysfunction.
2. The method of claim 1, wherein the level of DHT is increased to a concentration which is within, but not substantially exceeding, a normal range.
3. The method of claim 1, wherein the step of increasing the level of DHT comprises administering to the subject an effective amount of an exogenous dihydrotestosterone compound in a pharmaceutically acceptable carrier.
4. The method of claim 1, wherein the step of increasing the level of DHT comprises inducing accumulation of endogenous DHT.
5. The method of claim 4, wherein accumulation of endogenous DHT is induced by inhibiting metabolism of endogenous DHT.
6. The method of claim 4, wherein accumulation of endogenous DHT is induced by increasing production of bioavailable endogenous DHT.
7. A method for treating sexual dysfunction in a subject, comprising administering to the subject an effective amount of a dihydrotestosterone compound in a pharmaceutically acceptable carrier such that the sexual dysfunction is treated.
8. The method of claim 7 wherein the dihydrotestosterone compound is a derivative of dihydrotestosterone.
9. The method of claim 7 wherein the dihydrotestosterone compound is 5 $\alpha$ -dihydrotestosterone.
10. The method of claim 7 wherein the dihydrotestosterone compound is an analog of dihydrotestosterone.
11. The method of claim 7 wherein the sexual dysfunction is a dysfunction associated with hypogonadism.
12. A packaged composition for treatment of sexual dysfunction, comprising an effective amount of a dihydrotestosterone compound and a pharmaceutically acceptable

carrier, both packaged with instructions for using the effective amounts of the compound and the carrier as a treatment for sexual dysfunction.

13. A method for diagnosing and treating sexual dysfunction in a subject,  
5 comprising the steps of:  
identifying dihydrotestosterone deficiency in a subject afflicted with a sexual  
dysfunction; and  
increasing the level of dihydrotestosterone in the subject to effectively treat  
the sexual dysfunction.

10

**THIS PAGE BLANK (USPTO)**